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Placing Blame for the Vioxx Debacle

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Abstract

The purpose of this paper is to tell the complete story, from creation to termination to litigation, of the Merck Pharmaceutical Company drug, Vioxx. This paper will explain the type of drug Vioxx is and the way in which it was tested by researchers. It will outline the FDA drug review and approval process and briefly consider the debate between accelerated and traditional drug approval guidelines. It will then discuss the actions taken by the FDA in its review of Vioxx in 1999. It will paint a picture of the actions and negotiations which took place between Merck and the FDA after approval. Then it will discuss the decision by Merck to voluntarily withdrawal Vioxx from the market. It will then consider the ramifications of the withdrawal including the SEC and DOJ investigations, Congressional inquiry, and civil litigation. Finally, the paper will examine the pending litigation regarding Vioxx to determine the existence of themes and strategies in those cases as well as Merck's future post litigation.

Introduction

Robert Ernst was not your average 59 year old.¹ Ernst ran three to five miles a day. He competed in a number of Texas races including several marathons. In addition to his love of running, Robert Ernst was an avid bicyclist as well as a fitness class instructor. He met his wife Carol in 1997 at the gym where he worked in Cleburne, Texas.² The couple enjoyed staying physically active together. In April 2001, Carol and Robert teamed up to take part in the Beauty and the Beast bicycle tour, a six mile ride through Tyler, Texas.

While Robert had been both a smoker and a drinker, he kicked both habits almost twenty years earlier. His only health complaint was doctor diagnosed tendonitis in his hand. He first treated the pain with ibuprofen.³ Then in the fall of 2000, after a visit to his doctor, Robert switched to Vioxx to treat the pain in his hand. Carol said that taking Vioxx was much easier for her husband. Instead of taking multiple ibuprofen tablets, he needed to only take one 25 mg Vioxx pill each day.⁴ And for a long time, Robert appeared to suffer no “adverse reaction” to the drug.⁵

Then one afternoon about six months after he began taking Vioxx, Robert complained to Carol that his pulse rate seemed slower than usual after he finished his daily run. That night, May 6, 2001, after the couple had dinner at Olive Garden, watched some television, and went to bed, Robert’s breathing slowed to a very abnormal rate.⁶ Carol called 911 and Robert was rushed to Harris Methodist Walls Regional Hospital. He never regained consciousness.⁷

¹Kevin McCoy, *Merck to Face First Vioxx Trial Before Texas Jury Next Month*, USA Today. June 29, 2005.

²Ibid.

³Ibid.

⁴Ibid.

⁵Ibid.

⁶Ibid.

⁷Ibid.

The autopsy report concluded that Robert Ernst died of “cardiac arrhythmia secondary to coronary atherosclerosis.”⁸ Carol Ernst found Robert’s death to be a mystery; she could not believe her physically active husband could have died from a heart problem. So she began to investigate the possible causes. Eventually, she turned her investigation to Vioxx. Almost immediately, Carol came across a report linking several deaths in Great Britain to the pain killer.⁹

Carol became convinced that it was Vioxx that killed her husband. It was her belief that Merck & Company, the manufacturer of Vioxx was aware of the cardiovascular risks associated with the drug. She stated, “if they [Merck] had addressed those problems, Bob would still be here.”¹⁰ Carol Ernst sued Merck in 2002 in Brazoria County District Court in the state of Texas. The case against Merck was considered weak because in all the studies of Vioxx, the drug had not been linked to heart rhythm irregularities like the one Robert Ernst died from. But the coroner who performed the autopsy testified that there was a likelihood that Robert could have died of a blood clot not originally identified. Because she was unaware that Vioxx caused blood clots, the coroner stated that she did not thoroughly consider that cause of death when performing the autopsy.¹¹

After less than eleven hours of deliberation the Texas jury found Merck responsible for the death of 59 year old Robert Ernst. The jury awarded Carol Ernst \$253.4 million in punitive and compensatory damages.¹²

Ernst v. Merck & Co. was the first Vioxx case to go to trial and it was a huge victory for the plaintiff.

⁸Ibid.

⁹Ibid.

¹⁰Ibid.

¹¹Marc Kaufman, *Merck Found Liable in Vioxx*, Washington Post. August 20, 2005.

¹²Ibid.

The crushing court decision in the *Ernst* case and the thousands of other cases like it which are now pending has created tremendous interest in the Vioxx story. It is a long and complicated tale that often has sounds of a soap opera drama. The purpose of this paper is to sort through the story of Vioxx in an effort to better understand the overwhelming surge of litigation which has followed. This paper will begin with the creation of Vioxx by Merck. It will explain exactly what type of drug Vioxx actually is. It will discuss its intended uses. And, importantly, it will elaborate on the ways in which the drug was tested.

Next this paper will explore the path a new drug takes to the FDA and FDA review and approval process. It will consider how Vioxx was presented to the FDA and the manner in which the FDA examined its safety and efficacy. This paper will additionally elaborate on the criticism the FDA has received regarding its treatment of Vioxx.

After considering the role of the FDA, this paper will tell the story of what happened once Vioxx was placed on the market. It will discuss Merck's advertising scheme. It will also discuss its financial successes. And most particularly, this paper will explore the decision by Merck to withdraw Vioxx from the market. It was a decision that sent shockwaves through the drug industry as well as the government. And the withdrawal has had a major effect on the litigation which followed.

Finally, this paper will discuss the Vioxx litigation. It will consider some of the cases which have already been decided. It will also look forward to those cases which are pending in an effort to determine common themes. And it will offer predictions as to the way in which upcoming cases will play out and the effect they will have on Merck and the plaintiffs' bar.

As mentioned, it is a long and complicated story. But it is also an interesting one. To best understand that story, it is important to start at the beginning with the creation of the drug.

COX-2 Inhibitors and Vioxx

Vioxx is a COX-2 inhibitor. COX-2 Inhibitors belongs to a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDS).¹³ NSAIDS are commonly prescribed for the inflammation of arthritis and other body tissue. Traditional NSAIDS include Aspirin, ibuprofen or Motrin, naproxen, piroxicam, and nabumetone or Relafen.¹⁴ NSAIDS relieve pain by inhibiting enzymes called COX-1 and COX-2.¹⁵ COX-2 inhibitors are drugs for inflammation which selectively block the COX-2 enzyme. Blocking this enzyme challenges the creation of the chemical messengers, also known as prostoglandins that cause the pain and swelling of arthritis inflammation.¹⁶ Researchers had previously discovered that when COX-1 was blocked, there was interference with blood clotting and increased incidence of gastrointestinal events.¹⁷ Therefore, it was exciting to discover that COX-2 inhibitors appeared to avoid the gastrointestinal pitfalls associated with COX-1 inhibitors. Vioxx falls into the new class of COX-2 inhibitors with other drugs such as Celebrex.

Tests on Vioxx

A number of studies before but mainly after FDA approval of Vioxx were done to determine the safety and efficacy of the drug. It is important to have an understanding of these trials and the findings they produced because many of them have proved integral to the unfolding Vioxx saga. The first of these studies was VIGOR.¹⁸

VIGOR

¹³Overview of COX-2 Inhibitor Drugs. www.medicinenet.com/script.main.art.asp?articlekey=952&pf=3&page=1.

¹⁴Ibid.

¹⁵Ibid.

¹⁶Ibid.

¹⁷Ibid.

¹⁸Vioxx Timeline: Key Dates for VIGOR and Long-term, Placebo-controlled Studies Implemented to Provide Cardiovascular Safety Dates. Provided by Merck & Co.

As noted previously, COX-1 inhibitors were commonly associated with a high rate of adverse gastrointestinal (GI) events. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial was initiated to determine if rofecoxib or Vioxx would have lower GI events than traditional COX-I NSAIDS.¹⁹ The study which was published in 2000 (research was commenced in January of 1999) randomly assigned 8076 patients with rheumatoid arthritis who were at least fifty years old to either receive 50 mg of rofecoxib or 500 mg of naproxen, a traditional COX-1 NSAID, twice daily. The study lasted 12 months.²⁰

The results of the VIGOR study showed that Vioxx and naproxen were similarly effective at treating rheumatoid arthritis. Patients taking rofecoxib, however, experienced about 50% less GI events than those taking naproxen. Even though the gastrointestinal findings were the primary purpose of the study, they were quickly overshadowed. Instead, it was those findings which concerned cardiovascular (CV) incidents that received the most attention.²¹ The VIGOR study found that the incidence of myocardial infarction in rofecoxib patients was much higher than in those patients assigned to take naproxen.²² Patients taking naproxen had a heart attack rate of 0.1%. For patients taking Vioxx, the heart attack rate was 0.4%.²³

The elevated risk of cardiovascular events began during the second month on rofecoxib during the trial. There was no difference in the overall mortality rate or rate of cardiovascular deaths between the two groups.²⁴ And the difference in overall myocardial infarction only existed between the rofecoxib and naproxen patients who were already at higher risks for heart attacks.²⁵ There were also no differences in the lower risk groups according to the VIGOR results.

¹⁹Bombardier. *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 New England Journal of Medicine, 2000.

²⁰*Rofecoxib*. www.wikipedia.org/wiki/Rofecoxib.

²¹Ibid.

²²Ibid.

²³Ibid.

²⁴Bombardier. Ibid.

²⁵*Rofecoxib*. Ibid.

Scientists for Merck interpreted the elevated CV event rate for Vioxx users compared to users of naproxen to mean that naproxen had a protective effect against heart attacks.²⁶ In other words Merck contended that it was not that Vioxx created a higher rate of CV events; instead the rate looked higher next to naproxen because naproxen actually prevented such events and therefore had a lower than normal rate. In November of 2000 the VIGOR study was published in the New England Journal of Medicine (NEJM) over a year after FDA approval. In February of 2001 the results were presented to the FDA during a public hearing.²⁷

New England Journal of Medicine Controversy

More public attention was drawn to the Vioxx story as a result of the publication of the VIGOR study in the NEJM. A controversy erupted regarding an accusation made by the Journal's editors claiming that information presented by Merck to the FDA in 2001 had not been included in the November 2000 article. The editors claimed that "more than four months before the article was published at least two of its authors were aware of critical data on an array of adverse cardiovascular events that were not included in the VIGOR article."²⁸ This additional unreported data was said to include three heart attacks which if included in the trial would have raised the CV event risk of Vioxx to five times greater than naproxen.²⁹ It was also contended that the study published in the Journal did not report actual deaths even though it stated mortality rates between the two groups to be the same. All the additional unreported heart attacks occurred in the low risk of heart attack group known as the "aspirin not indicated group."³⁰ The results of these data omissions, the

²⁶www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2.06_cardio.pdf

²⁷ *Rofecoxib*. Ibid.

²⁸ www.content.nejm.org/cgi/content/extract/353/26/2813

²⁹ Ibid.

³⁰ Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., and Schnitzer, T. J., Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group, *N Engl J Med*, vol. 343, no. 21, pp. 1520-8, 2, Nov.2000.

editors argued “resulted in the misleading conclusion that there was a difference in the risk of myocardial infarctions between the aspirin indicated and aspirin not indicated groups.”³¹

The VIGOR study authors responded to contentions of the NEJM editors by claiming that the three additional heart attacks happened after the pre-determined study end date. They also stated that the omitted information in no way fundamentally changed the ultimate conclusions of the study.

Alzheimer’s Study

Beginning in February of 1999 Merck conducted several studies of rofecoxib in order to determine if the drug slowed the onset of Alzheimer’s disease. These trials were relatively large studies with close to 3000 patients and they compared Vioxx to a placebo rather than to another drug, unlike the comparison to naproxen in the VIGOR study.³² While these studies did show a higher death rate among users of rofecoxib patients, the deaths were generally not cardiovascular.³³ Also, the Alzheimer’s studies did not show an increase in cardiovascular events among Vioxx users. For these reasons, Merck has readily pointed to these studies to prove Vioxx safety and to refute other evidence to the contrary.

APPROVe Study

In 2001 Merck commenced the Adenomolous Polyp Prevention on Vioxx (APPROVe) study. APPROVe was a three year trial with the main goal of evaluating the “efficacy of rofecoxib for prophylaxis of colorectal

³¹Ibid.

³²*Rofecoxib*. Ibid.

³³Ibid.

polyps.”³⁴ At the time the study commenced, it was known by researches that precancerous tissues also produce COX enzymes. Therefore, scientists wanted to explore the possibility of inhibiting those enzymes in an effort to stop or slow cancer growth.³⁵

Specifically, the APPROVe study was used to determine if 25 mg of Vioxx could prevent the reoccurrence of colon polyps in patients with a history of colorectal adenomas which are benign tumors in the large intestine.³⁶ An additional aim of the study was to, again, evaluate the cardiovascular safety of rofecoxib.³⁷ The APPROVe trial was a randomized trial of 2586 patients receiving either 25 mg of Vioxx per day or a placebo within twelve weeks of surgical resection of colorectal polyps and after three years of treatment.³⁸ The study ended early, however, and for that reason no report was produced regarding Vioxx’s ability to reduce the risk of colon cancer.³⁹

The study ended prematurely when initial data revealed an increased risk of adverse cardiovascular events. The increased risk began after eighteen months of taking rofecoxib.⁴⁰ In those patients taking Vioxx, there were 1.50 cardiovascular events per 100 patient years. Alternatively, those patients taking the placebo suffered only 0.78 cardiovascular events in the same period of time.⁴¹

The Cleveland Clinic Study

³⁴Ibid.

³⁵*Prescription for Trouble*. Ibid.

³⁶Anonymous. *Cardiovascular Risk of Selective COX-2 Inhibitors...Fact or Fiction?* Johns Hopkins Arthritis Forum. http://www.hopkins-arthritis.som.jhmi.edu/news-archive/2005/cardiac_risk.cox2.html#approve

³⁷*Rofecoxib*. Ibid.

³⁸Ibid.

³⁹Ibid.

⁴⁰Ibid.

⁴¹Ibid.

The Cleveland study was a retrospective study used to determine the accuracy of the previous test finding which showed that COX-2 inhibitors did in fact increase the risks of cardiovascular events.⁴² The study was headed by Doctors Mukherjee, Nissen and Topol of the Department of Cardiovascular Medicine of the Cleveland Clinic. The results of the study appeared in the Journal of the American Medical Association. The Cleveland Clinic Trial tested Celebrex, the Pfizer COX-2 NSAID, as well as Vioxx. The trial was unique in that its method of analysis was to study four previous randomized, double-blind trials of COX-2 inhibitors published between 1998 and February of 2001.⁴³ The trials analyzed by the Cleveland Clinic included the VIGOR study, Study 085, and Study 090. Study 085 and Study 090 were small clinical trials done in house by Merck which occurred prior to the VIGOR trial and prior to FDA review and approval. The results of those studies were not made public until they were later published in an FDA memorandum.⁴⁴

The largest study analyzed in these trials was VIGOR. The VIGOR study had previously demonstrated a dramatic increase in cardiovascular event rates in patients taking rofecoxib compared to those patients taking naproxen.⁴⁵ However, the “absolute incidence” documented in that study was 1.3% for the rofecoxib group and 0.67% for the naproxen group. Studies 085 and 090 were smaller, placebo-controlled studies.⁴⁶ Study 085 compared the efficacy and safety of rofecoxib with the placebo after six weeks of treatment for osteoarthritis in the knee. There were a total of three CV events during the study, all of which took place in the rofecoxib test group. Study 090 was identical to Study 085 but was not limited to six weeks.⁴⁷ In Study

⁴²Mukherjee, D., Nissen, S. E., and Topol, E. J., Risk of cardiovascular events associated with selective COX-2 inhibitors, JAMA: The Journal of the American Medical Association, vol. 286, no. 8, pp. 954-959, Aug.2001.

⁴³Ibid.

⁴⁴Ibid.

⁴⁵Ibid.

⁴⁶Ibid.

⁴⁷Ibid.

090, there were nine recorded CV events and six were from the rofecoxib group.

The Cleveland Clinic trial research compared these trial results with four large trials of aspirin and placebo for prevention of heart attacks.⁴⁸ The trials involved 48,450 patients. The findings of the Cleveland Clinic were startling. The heart attack rate for the placebo group was 0.50% whereas the rate for the rofecoxib group was 0.74%.

The Lancet Study

Dr. David Graham, associate director for science at the Food and Drug Administration's Office of Drug Safety, published a study in January of 2004 in the British medical journal *The Lancet*. The study examined the risks of COX-2 drugs of which Dr. Graham had been a long standing critic. The findings of his study only reinforced his long standing objection to the safety of the drug.

Dr. Graham and his team of researchers initiated the study for the purpose of determining whether the risk of serious CV events was increased in those patients taking rofecoxib or Vioxx.⁴⁹ To make this determination the researchers used the California managed-care patient database as the group of test patients. The database included 1.4 million patients. The study was observational and retrospective. It looked at all those patients who filled at least one prescription for a COX-2 inhibitor (the study also looked at Celebrex) between January

⁴⁸Ibid.

⁴⁹Memorandum from Dr. David Graham, Director of Science, Office of Drug Safety to Dr. Paul Seligman, Director, Office of Drug Safety. Re: Study entitled "Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with COX-2 Selective and Non-Selective NSAIDS." <http://www.fda.gov/cder/drug/infopage/vioxx/vioxxgraham.pdf>

1999 and December 31, 2001.⁵⁰ The study then recorded the number of cardiovascular events experienced by those patients.

Overall, the study found that those patients taking Vioxx had a 59% higher risk of CV events than those patients taking other COX-2 inhibitors such as Celebrex.⁵¹ It also found that those individuals taking a lower dose of rofecoxib had only a 42% increase. Whereas those taking higher doses had a 360% increase.⁵² Dr. Graham also noted that the five-fold increase of CV event risk found in the VIGOR study could not be attributed to naproxen's preventative effect as previously argued by Merck scientists.⁵³ Instead, Dr. Graham's study found that patients taking naproxen had a 14% increased rate of cardiovascular events.⁵⁴

A great deal of controversy surrounded *The Lancet* study. Some researchers have contended that the study possessed significant flaws. One obvious flaw was that Dr. Graham identified only those patients who had been prescribed COX-2 inhibitors. That group of patients is already at a higher risk of heart problems. Therefore, data showing an increase in CV events among those selected patients could be misleading given their existing proclivity for such incidents.

In addition to research related problems, the publication of this study placed Dr. Graham in the media spotlight. The study was originally to be published on the eve of his testimony before congress regarding the FDA's handling of the Vioxx approval process (to be discussed later). While the paper was withdrawn from publication at that time and not printed until some three months later, it was still considered an effort

⁵⁰Ibid.

⁵¹Ibid.

⁵²Ibid.

⁵³Ibid.

⁵⁴Ibid.

on the part of Dr. Graham to confirm and reinforce the points he intended to make to Congress concerning the risks associated with Vioxx. Dr. Graham argued that he had previously recognized the harm that Vioxx presented but that the FDA had ignored his position. It is not at all surprising that the FDA did not want *The Lancet* study published given that it concluded that between 88,000 and 140,000 incidents of serious CV events are likely to have been caused by the drug.⁵⁵

Conclusions about the Vioxx Studies

An understanding of the research done on Vioxx is critical because much of the debate concerning Vioxx has involved the findings of each of these studies and trials. It is clear that each study found that Vioxx increased, to some degree, the risk of cardiovascular events in those patients taking the drug. Therefore, the most important issues to be considered regarding these tests are: when were the test results available, how were the results interpreted, and who was privy to the results. Critics of Merck such as Dr. Topol, of the Cleveland study, claim that the company had the results of smaller studies such as Studies 090 and 085 prior to FDA review, which showed an increase in CV events but refused to publish them.⁵⁶ Therefore, it could be argued that Merck should have not presented the drug for FDA approval until it confirmed or refuted the findings (later, of course, the findings were confirmed in the VIGOR study). On the other hand, some point the finger at the FDA. It is argued that while the majority of the previously mentioned test results were not available at the time Vioxx was being considered for market approval, the FDA was too quick to approve Vioxx. The FDA could have waited for more results to become available. And even after market approval, as the test results did become available, the FDA was too slow to consider the appropriate response to the findings. To best determine if these criticisms of the FDA are warranted, an understanding of the FDA's

⁵⁵Ibid.

⁵⁶*Prescription for Trouble*, CBS News, www.cbsnews.com. August 28, 2005

approval process is necessary.

The Food and Drug Administration

Almost seventy years ago, Congress passed the Food, Drug, and Cosmetic Act (FDCA) of 1938. The FDCA was passed in an effort to reform the failing drug industry. Specifically, the FDCA was drafted in response to the death of more than 100 people who perished from drinking Elixir Sulfanilamide, a form of sulfa medicine that was manufactured and sold in the United States.⁵⁷ Before the FDCA, the Food and Drugs Act of 1906 required only that drugs meet a standard of “strength and purity.”⁵⁸ Under the FDCA, however, manufacturers had to prove the safety of any drug to be sold across state lines. Twenty-four years later, again efforts were made to improve the drug manufacturing process. In 1962, Tennessee Senator Estes Kefauver became concerned with negligence in the pharmaceutical industry after a drug manufactured in Germany and sold throughout Europe was known to cause serious birth defects in the children of mothers who took the drug.⁵⁹ His attention to this problem resulted in the writing of the Kefauver-Harris Amendments also known as the Drug Amendments Act of 1962. The Act required drug manufacturers to establish the “safety and effectiveness” of all drugs in the market.⁶⁰ The Act also made the FDA responsible for regulating the drug industry.

Today the FDA is a major player in the drug industry. The job of approving prescription drugs belongs to

⁵⁷“United States Drug Approval Process.” www.imaginis.com/breasthealth/drug_approval.asp?mode=1

⁵⁸Ibid.

⁵⁹Ibid.

⁶⁰Ibid.

the FDA's Center for Drug Evaluation and Research (CDER). Prior to entering the marketplace CDER must approve all new prescription drugs. The process of drug development and review is lengthy and complicated and it begins with pre-clinical research.

Pre-Clinical Research

There are several ways in which a new drug is developed. Research generally begins broadly, often with scientists considering the fundamentals of the human body and the way in which it functions. Ideas are then developed regarding new ways to treat illnesses and abnormalities.⁶¹ Researches then begin to search for compounds that will help achieve the desired, hypothesized results. The experimental drug, once created, is tested to determine how well it works and what, if any, adverse effects it could potentially produce.⁶² It is during the pre-clinical stage that short term animal testing occurs.⁶³

Researchers try to use as few animals as possible in these tests. A variety of species are often tested for the purpose of determining how the drug is absorbed and chemically broken down once it enters the blood stream of different organisms.⁶⁴ These tests also examine the toxicity of the drug and the length of time it remains in the body. The results of the pre-clinical tests are then used for the purpose of submitting an Investigational New Drug (IND) application to CDER.⁶⁵ CDER reviews the application and its supporting data to determine if the drug is safe enough to be tested on humans in the clinical studies stage.

Clinical Studies

The main purpose of stage two clinical studies is to determine the safety and efficacy of the proposed drug

⁶¹Ibid.

⁶²*The Drug Approval Process: How Drugs Come to Market.* Rx Times.

⁶³Ibid.

⁶⁴Ibid.

⁶⁵Ibid.

through the use of tests on humans.⁶⁶ These human tests are most often done at universities, cancer centers, hospitals, or private clinics.⁶⁷ The clinical studies consist of several phases. Phase I tests the experimental drug on healthy subjects who do not have the illness which the drug is proposed to help. This testing takes an average of six months to one year and it is conducted for the purpose of establishing how a healthy body responds to the drug, possible side effects, and the appropriate dosage to be recommended.⁶⁸

Phase II allows researchers to test the drug on patients who suffer the illness to be treated by the drug.⁶⁹ The patient group here is larger than the one tested in Phase I and the testing generally lasts twice as long.⁷⁰ If at least one-fifth of the patients respond well to the drug then the drug is considered effective. If effective, then studies on the drug can advance to Phase III.

In Phase III, the sponsors of the drug are expected to meet with officials at the FDA to set-up the parameters of Phase III testing.⁷¹ This is the most important round of testing because the number of patient participants can range from several hundred to several thousand.

The broad size of these studies allows for more accurate data regarding safety and efficacy.

After the different phases of stage two is stage three, which is the FDA review and approval process. In this stage, the drug sponsors must bring together all the information and data collected during the testing and must submit that information in a formal application to the FDA called a New Drug Application (NDA). The NDA is often very thorough and can run more than 1,000 pages in length.⁷² The FDA then reviews all the information presented in the application and considers the risks versus the benefits of approving the drug. If necessary the FDA can suggest further testing be conducted on the drug if it seems that there is not enough data to make a decision on approval one way or the other.⁷³ The proposed labeling of the drug

⁶⁶“United States Drug Approval Process.” Ibid.

⁶⁷Ibid.

⁶⁸*The Drug Approval Process.* Ibid.

⁶⁹Ibid.

⁷⁰Ibid.

⁷¹Ibid.

⁷²Ibid.

⁷³Ibid.

is also reviewed and subject to approval. While the review process can last as long as seven to thirteen years, recently, the review time has been reduced significantly.⁷⁴ CDER, which serves as the primary review board in the approval process, in general terms, asks and considers the answers to two basic questions when considering the approval of a new drug: 1- “Do the results of clinical studies provide substantial evidence of the drugs effectiveness?” and 2- “Do the results of clinical studies show that the drug is safe under the proposed labeling.”⁷⁵

If a drug is approved, it is then marketed and sold to the general public. At that point there is often a Phase IV follow-up study.⁷⁶ Whether or not a Phase four study is initiated is entirely in the FDA’s discretion. Now, more often than not, these studies always take place for new drugs. Phase four is used as a monitoring device that helps to track side effects and any other adverse complications associated with the drug once it is prescribed to the general public.⁷⁷ If the findings of a Phase four study are unsatisfactory, the FDA can withdraw approval of the drug.

Accelerated v. Traditional FDA Approval

As discussed earlier, the Food and Drug Administration’s mission is to serve and protect the public interest by regulating and ensuring the safety and efficacy of drugs and medical devices.⁷⁸ The scope of the FDA’s power

⁷⁴Ibid.

⁷⁵Ibid.

⁷⁶Melissa Marie Bean. *Fatal Flaws in the Food and Drug Administration’s Drug Approval Formula*. Utah Law Review. 2003 Utah L. Rev. 881

⁷⁷Ibid.

⁷⁸FDA Mission Statement. <http://www.fda.gov/opacom/morechoices/mission.html>

is far reaching. It controls the clinical research, approval, and advertising language of new pharmaceuticals.⁷⁹ In performing its function as overseer, the FDA has been historically very cautious and thorough.

In the 1980s, however, the AIDS crisis called for a new approach to drug approval.⁸⁰ The epidemic generated a strong lobbying group which demanded that Congress allow for the FDA to speed up the review process for drugs which could prove to be life-saving.⁸¹ The lobbying effort was successful. Congress drafted section (h) of C.F.R. 314.500 which provided for “fast track” approval of drugs used to treat “serious or life-threatening illness and that provide meaningful therapeutic benefit to patients over existing treatments.”⁸² The effects of the new approval process were immediate. In 1987, approval time for a new drug was over two years. In 1992 the approval time was nineteen months.⁸³ The success of the AIDS lobbyists was the catalysts for cancer activists to seek similar treatment for their own drugs. In response to the increased rallying cry for continued acceleration of the drug approval process, Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA).

The FDAMA was similar to C.F.R. 314.500. It established three levels of the drug approval process. The first is a “fast-track” designation for drugs used to treat life-threatening illnesses or an illness for which there are currently no treatments available.⁸⁴ A drug given fast-track designation receives approval in six months or less. The second level created by FDAMA is “priority review” which provides approval in twelve months or less for those drugs that also treat life-threatening illnesses. And finally, the third level which is the “accelerated level” provides for traditional approval times (but still considerably faster than traditional

⁷⁹Melissa Marie Bean. Ibid.

⁸⁰Ibid.

⁸¹Ibid.

⁸²21 C.F.R. 314.500

⁸³Melissa Marie Bean. Ibid.

⁸⁴21 USC 356, Sect. 506.

approval times of the decade previous).⁸⁵ The FDAMA also established a system where pharmaceutical companies pay the FDA a fee to ensure that there are enough employees to make this expedited approval process happen.

The changes called for by activists fighting life threatening diseases and those implemented by the Congress were all in an effort to ensure that medical advancements in drug treatments were not kept from those patients most in need because of bureaucratic delay. It seems that at the time when AIDS was killing countless people, there was an idea that the FDA had the cure for the disease but was simply not releasing it to the public. The acceleration of the approval process was an effort to shatter that image. In the years since the changes took effect, however, new concerns have surfaced. Many critics argue that the FDA's efforts to speed up and improve the approval process have gone too far and at the price of safety.

One major complaint with the new FDA system is that it puts the FDA in the pocket of the pharmaceutical companies. Because the manufacturers pay the FDA fees it is argued that they will feel entitled to an expedited review. And the FDA may in fact feel obligated to approve drugs too quickly or to approve drugs that should not be approved at all.⁸⁶ While a healthy working relationship between the FDA and the pharmaceutical industry is undoubtedly important, some critics argue that they should not become too close. The mission of the FDA is to guarantee that only safe and effective drugs enter the market. The argument follows that an FDA under the influence of pharmaceutical companies might fail in that mission.

In addition to concerns over FDA manipulation critics of the new approval system also claim that expedited review is often granted to drugs not used to treat life-threatening illnesses.⁸⁷ Including more drugs for priority review will also undermine the FDA mission of consumer protection.

⁸⁵Ibid.

⁸⁶Melissa Marie Bean. Ibid.

⁸⁷As will be discussed later, a good example of this fact is Vioxx. It received priority review but it was submitted for approval only to treat acute pain and arthritis- not a life-threatening illness.

Critics of the new accelerated drug approval timeline also argue that the expedited process has caused the FDA to approve unsafe drugs. In order to act within the required window of time, the FDA might approve a drug too hastily. Some FDA research officials have complained that they have felt pressure to approve drugs that they felt did not warrant approval.⁸⁸ Since the expedited drug approval system was enacted, the FDA has approved 80% of drugs submitted for review as opposed to only 60% in the early 1990s.⁸⁹ It is also contended that the FDA has become more willing to go forward with approval even when the requisite scientific data is unavailable.

Supporters of the accelerated drug approval process, on the other hand, have strong arguments on their side. First, it is argued that without an accelerated system for the most necessary drugs, many terminal patients would be without possible life-saving medicines. As mentioned earlier it was AIDS advocates who initiated the outcry for a speedier drug approval process. It was argued that the regulatory constraints on the drug approval process were costing peoples' lives by holding up a drug's placement on the market.

Also, there is a free market argument in support of fast track FDA drug approval. That argument contends that there are strong incentives on the pharmaceutical companies to only present to the FDA those drugs which actually merit approval. If a pharmaceutical company submits a drug to the FDA for priority review and that drug, after it is approved, it is found to be unsafe or dangerous to the public, the pharmaceutical company will suffer.⁹⁰ Therefore, no company would want to submit an unsafe drug for approval. The Vioxx story illustrates each of the arguments both for and against accelerated drug approval.

⁸⁸Ibid.

⁸⁹Ibid.

⁹⁰Vivian I. Orlando. *The FDA's Accelerated Approval Process: Does the Pharmaceutical Industry Have Adequate Incentives for Self-Regulation*. American Journal of Law and Medicine. 25 Am. J. L. and Med. 543

FDA Review and Approval of Vioxx

The FDA approved Vioxx in May of 1999. It was approved for the primary purpose of reducing the signs and symptoms of osteoarthritis as well as for treating acute pain in adults.⁹¹ Vioxx received a “priority review” because “the drug potentially provided significant therapeutic advantage over existing approved drugs due to its fewer gastrointestinal side effects.”⁹²

Prior to its approval, Vioxx was presented to and reviewed by the FDA Arthritis Advisory Committee on April 20, 1999. At the Committee hearing, Merck researchers presented their case for Vioxx and the FDA researchers followed with their comments. In the original review of the drug, there was a safety database of around 5000 patients.⁹³ In the clinical trials the risk of gastrointestinal events was significantly lower in the patients taking Vioxx. And importantly, the trial data available to the FDA at the time the Vioxx review in 1999 did not show an increase in cardiovascular events.

The Arthritis Committee unanimously approved Vioxx. However, the committee did have some concerns. The major concern voiced was that patients would take more of the drug than was approved for dosage. This practice is called “dose creep.” Clearly it is impossible to monitor the patient intake of any drug but the concern over dose creeping was particularly high with Vioxx.⁹⁴ The elevated concern was due to the fact that some data showed dose-related toxicity. 12.5 mg was the suggested dose amount but it was thought that some patients could go as high as 25 mg per day. Doses higher than 50 mg per day, however, could

⁹¹Statement of Sandra Kweder, MD. November 18, 2004. <http://www.fda.gov/ola/2004/vioxx1118.html>

⁹²Ibid.

⁹³FDA CDER, Transcript of Arthritis Advisory Committee, Review of NDA #21-042, Apr. 20, 1999 at <http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3508t1.rtf>.

⁹⁴Ibid.

cause problems for many patients. The Arthritis Committee therefore considered the option of allowing the drug's label to reflect the information that risk to the patient increased with dosage amount.⁹⁵

An additional concern considered by the committee was also one regarding dosage amount. The committee considered the issue of using Vioxx for the treatment of acute pain.⁹⁶ It was decided that because the adverse effects found in the clinical studies did not kick in until after five days of use, 50 mg per day for five days could be used to treat acute pain. After five days, use of Vioxx would need to be stopped.⁹⁷ The majority of the committee also agreed that Vioxx labeling should note that patients taking 50 mg per day for acute pain could experience adverse side effects.⁹⁸

As mentioned earlier, the committee unanimously recommended that Vioxx be approved. The drug was approved for the relief of signs and symptoms of osteoarthritis, acute pain, and the treatment of menstrual cramps.

Post Approval Actions by FDA and Merck

Once it was approved for the market, Merck began an aggressive advertising campaign. The company spent over \$500 million on direct-to-consumer and direct-to-physician advertisements and promotions.⁹⁹ This money equaled more than \$5 for each prescription written since the drug entered the market in 1999. In 2001, more money was spent on advertisements for Vioxx than for any other drug. Merck promoted Vioxx as a much more effective NSAID than those already on the market; a claim that later was proved false. And while at first the FDA required a gastrointestinal warning label on the drug, that warning was removed in 2002 when the results of the VIGOR study were released.

⁹⁵Ibid.

⁹⁶Ibid.

⁹⁷Ibid.

⁹⁸Ibid.

⁹⁹ "Vioxx: Birth and Death of a Super Aspirin." Cindi Solomon and Sandy Summers. Mealey's Litigation Report: Arthritis Drugs. November 2004. 1-6.

After approval of Vioxx, Phase four monitoring of the drug commenced. On March 30, 2000 the FDA received its first batch of troubling data. At that time, preliminary information regarding an increase of cardiovascular events among Vioxx users compared with other patients was submitted.¹⁰⁰ Then, later that year in June, the findings of the VIGOR study were presented by Merck to the FDA. The study, as discussed earlier, found a decrease in gastrointestinal side effects but an increase in cardiovascular problems among rofecoxib users. It was not until February 8, 2001 that the Arthritis Advisory Committee met to discuss the VIGOR study results.¹⁰¹ The committee noted the appearance of increased CV events but agreed with Merck's explanation that naproxen had a preventative effect and thought only that the findings needed further study.¹⁰² The benefit of lower gastrointestinal events was evidently viewed by the committee as a benefit that should be weighted heavily against any risks.¹⁰³

After the findings of the Arthritis Committee, the FDA requested additional information from Merck including further study findings. On July 12, 2001 Merck met this demand and submitted additional data on the cardiovascular risk posed by Vioxx. In response to the findings, the FDA initiated the previously discussed study conducted by Dr. Graham.¹⁰⁴ The FDA also began negotiating with Merck for a Vioxx label change.¹⁰⁵ On November 6, 2001 Merck rejected the FDA's proposed labeling and Merck countered with a different label change. The FDA decided that a face to face meeting with Merck was the only way to approach the problem of the label change. Several meetings ensued between the parties and a final label

¹⁰⁰<http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1.04.E-FDA-TAB-C.htm>. FDA Vioxx Timeline.

¹⁰¹Ibid.

¹⁰²Ibid.

¹⁰³Ibid.

¹⁰⁴Ibid.

¹⁰⁵Ibid.

was not introduced until March 20, 2002, almost two years after the FDA first received initial data showing an increase in cardiovascular rates.¹⁰⁶

On February 28, 2003 the FDA and Merck met to discuss the findings of the Alzheimer study as well as early polyp study findings.¹⁰⁷ Concerns over the heightened cardiovascular event rate were considered by both sides. In December of the same year, despite these concerns, Merck submitted an application to the FDA to consider Vioxx for the treatment of Juvenile Rheumatoid Arthritis (JRA).¹⁰⁸ On September 27, 2004 Merck was scheduled to brief the FDA on the current status of the Alzheimer study as well as studies supporting the petition to approve Vioxx for treatment of JRA. That briefing never took place. That same day Merck received the news that the data from the APPROVe study showed an increased risk of myocardial infarction and stroke.¹⁰⁹ On September 30, 2004 Merck publicly announced the worldwide withdrawal of Vioxx.

Criticism of the FDA

At the time of the original Vioxx approval hearings, the information presented to the FDA and the arthritis committee was limited. The vast majority of the major studies done on the safety and efficacy of Vioxx came after the 1999 approval. In spite of the now apparent lack of information and data on safety, the FDA proceeded in an accelerated manner to approve Merck's Vioxx. The handling of the approval process on the part of the FDA has generated a great deal of criticism. This criticism in many ways reflects the general

¹⁰⁶Ibid.

¹⁰⁷Ibid.

¹⁰⁸Ibid.

¹⁰⁹Ibid.

debate over accelerated approval. Vioxx received priority review even though it was not intended for the treatment of any life-threatening illness. Additionally many claim that the FDA approved Vioxx without requisite scientific data. There were a number of studies that were ongoing but incomplete at the time Merck presented the drug for FDA review. Instead of waiting for the findings of those studies, the FDA approved the drug on the basis of the minimal data available.

In the aftermath of the Vioxx story, there was finger pointing to both the FDA and Merck as the negligent party. Determining where fault lies is complicated and has no precise answer.

Were the actions of the FDA appropriate?

From the perspective of hindsight, it is easy to say that the FDA should not have approved Vioxx. However, it is important to consider the position the FDA was in at the time of the approval process. The FDA believed that while Vioxx was not going to treat life-threatening illnesses, it was considered unique in its ability to treat arthritis and acute pain without the gastrointestinal side effects. As Dr. Sandra Kweder, acting director of the Office of New Drugs noted in her congressional testimony, “the general standard for a priority review is applied when something is considered to have the potential to provide a clinical or therapeutic advantage, and, in the case of Celebrex and Vioxx, it was hoped and expected that these drugs would provide an important G.I. safety advantage.”¹¹⁰ The FDA did however, make mistakes. It is clear that the FDA approved the drug prior to the conclusion of the most significant safety studies. Even after the FDA in 2000 was presented with the VIGOR study which showed an increase in heart attacks among Vioxx users, it was not until many months later that Merck was advised to begin long term trials to further

¹¹⁰Statement of Sandra Kweder, MD. November 18, 2004. <http://www.fda.gov/ola/2004/vioxx1118.html>.

test for the cardiovascular effect of Vioxx on patients.¹¹¹ Additionally, although it was believed to be unique in its ability to treat acute arthritic pain, there were other drugs on the market used for that purpose. If Vioxx had not been given a priority review, the FDA would have had the time to wait for the initial results of the major studies and the evidence of adverse cardiovascular occurrences associated with the drug might likely have been discovered before it went on the market. And while the FDA and the Arthritis Committee were thorough in their questioning and review of Merck regarding the limited data and study findings they produced, the FDA should have demanded much more information before the drug was approved. The FDA gave so much weight to Vioxx's gastrointestinal benefits that it all but ignored the cardiovascular risks of the drug.

Were Merck's actions appropriate?

The most important question to answer when considering if the actions of Merck were appropriate is what information Merck had regarding increased cardiovascular events when it presented the drug for FDA approval. After the withdrawal of Vioxx from the market (to be discussed in detail later) it was discovered through various investigations that Merck had some evidence of increased cardiovascular risks prior to the 1999 FDA review and approval, including specifically Study 085 and Study 090. It was also shown that at the time Merck presented the drug for review, the larger and more long-term studies were not completed. Only a very small number of patients taking the drug for over a full year had been observed.¹¹² And yet, Merck still proceeded to petition the FDA for market approval. It was irresponsible and very dangerous to seek market approval for a drug that had some warning signs of cardiovascular risks. Merck should have waited until the conclusion of its larger studies such as the VIGOR trial before it decided how to proceed

¹¹¹The delay by the FDA in pressuring Merck to re-label the product was considered in detail during the congressional hearings and investigation and will be discussed later in this paper.

¹¹²This is an important point because the strongest scientific evidence shows most cardiovascular health risks are associated with Vioxx use of over eighteen months.

with Vioxx.

Merck Withdrawal

The Vioxx story was complicated and tenuous from the beginning but then in September of 2004 it became even more unusual when Merck voluntarily recalled the drug off the market. In the years after the 1999 approval of Vioxx, Merck was very confident in the strength of the drug. It was so confident that it wanted to expand the use of the drug to include the treatment of colon polyps. The APPROVe study, described in detail earlier, was undertaken to determine if Vioxx was effective in treating and/or preventing colon cancer.¹¹³ The APPROVe study was hoped to initiate an expansion of the drug's uses but instead the results of that test initiated the beginning of the end for Vioxx.

The APPROVe study was stopped around the eighteen month mark when results showed an increase in cardiovascular events. The CV events were double that found in patients taking the placebo.¹¹⁴ When similar findings came out of the VIGOR test, Merck was able to attribute the increase in CV events to the fact that naproxen had a protective effect against heart attacks. Because the patients in the APPROVe study took a placebo, no such claim could be made.¹¹⁵ Presumably unaware of another course of action, Merck withdrew Vioxx.

The staggering effects of the withdraw were only heightened when, on the same day of the announced withdraw, Dr. David Graham Associate Director of Science in the FDA's Office of Drug Safety, published

¹¹³ *Rofecoxib*. Ibid.

¹¹⁴ "Vioxx: Birth and Death of a Super Aspirin." Solomon and Summers. Ibid.

¹¹⁵ "Vioxx: Birth and Death of a Super Aspirin." Solomon and Summers. Ibid.

his memorandum which detailed the results of a study he conducted on Vioxx (those results were published in the British journal *Lancet* as discussed previously).¹¹⁶ In that memorandum, Dr. Graham concluded that over 27,000 more patients taking Vioxx may have had heart attacks and/or died as compared with those taking the milder drug Celebrex.¹¹⁷ While working with the FDA, Graham was in charge of investigating the cardiovascular impact of NSAID drugs.¹¹⁸ He claimed that the FDA stifled his efforts to publish the results of his studies.¹¹⁹

The September 30, 2004 withdrawal of Vioxx brought difficult times for both Merck and the FDA. Much discussion and debate has centered on the decision by Merck to voluntarily withdraw the drug. Some arguments have been made that the withdrawal was beneficial to Merck's cause. It can also be argued, however, that in fact the voluntary withdrawal of Vioxx was anything but positive for the drug manufacturer. Merck's decision to withdraw Vioxx from the market was done voluntarily and came before any such demand was made by the FDA. First it is important to note that by voluntarily pulling a drug, the possibility of the drug reentering the market at a later date is kept open.¹²⁰ It is possible that Merck wanted to have the option of reintroducing the drug at a later time after pursuing more vigorous studies into its safety. A more likely rationale for the voluntary recall was a litigation strategy. After the recall of any drug litigation is undoubtedly going to follow and it is generally believed that a drug manufacturer that independently chooses to remove its product from the market will receive a better reception from juries in future litigation.¹²¹ The reason for this is simple; it shows that the manufacturer is acting responsibly and with the interest of public safety as the priority. Therefore, if Merck finds sympathy from juries its decision will provide it some benefit. However, whether that benefit will outweigh the cost of the recall is doubtful because the costs appear to

¹¹⁶Ibid.

¹¹⁷Ibid.

¹¹⁸Ibid.

¹¹⁹Ibid.

¹²⁰Richard Epstein. Ibid.

¹²¹Ibid.

be great.

The recall of Vioxx by Merck has been treated by public opinion not so much as the act of a responsible drug manufacturer but instead as an admission of negligent conduct.¹²² As mentioned, the withdrawal was accompanied by an onslaught of editorials and memoranda on the part of researchers and scientists, such as Dr. Graham of the FDA, stating the dangers associated with the drug. The financial repercussions were immediately felt as well. The day it announced the recall, Merck shares were at \$45.07. By the end of the day they fell \$12 to \$33 per share.¹²³ It was not long before there was talk of a possible merger.¹²⁴

In addition to the decline in Merck's market standing, the recall of Vioxx also led to more long term problems. The withdrawal was closely followed by investigations by both the Securities and Exchange Commission (SEC) and the Department of Justice (DOJ). There was also a strenuous Congressional investigation and hearings. And there was an immediate flood of litigation. This paper will consider each of these effects in turn, beginning with the investigation by the SEC.

SEC Investigation

Because Merck is a publicly held company with shares held by both individual shareholders as well as institutional investors, the SEC is responsible for protecting those interests.¹²⁵ A publicly held company can be held liable if it at any time it misled investors about important information regarding the company or its product. Following the withdrawal of Vioxx, Merck share prices dropped substantially. And since that time, Merck's market value declined by billions of dollars, dramatically effecting investors and shareholders.

¹²²Ibid.

¹²³Ibid.

¹²⁴Ibid.

¹²⁵"Vioxx, Celebrex, and Bextra Recall News." <http://www.mynippon.com/vioxx/2005/01/sec-investigates-vioxx-recall-by-merck.html>.

In November 2004, the SEC began an “informal” investigation into the pharmaceutical manufacturer and by January 28, 2005 Merck announced that the investigation had been elevated to a formal one.¹²⁶ The decision was a serious blow for Merck.¹²⁷

In a formal investigation, the SEC has the authority to subpoena witnesses to testify to the handling of the Vioxx situation by Merck. While the SEC has a policy of not divulging any information regarding their formal investigations, the subject of their inquiry is fairly obvious. The SEC is likely interested in determining when Merck became aware of the cardiovascular risks associated with Vioxx. This information is important because Merck would have been obligated to inform the investors and shareholders of such a serious problem that would have undoubtedly affected the value and strength of the company and its stocks. The findings and results of that investigation which began over a year ago have not yet been disclosed.

Department of Justice Investigation

In addition to the SEC investigation of Merck’s dealings with shareholders and investors, in January 2005 the Department of Justice began a criminal investigation into the pharmaceutical company’s dealings.¹²⁸ At the heart of the DOJ investigation is again the extent of Merck’s knowledge of Vioxx’s adverse health risks. After the September 2004 recall, much evidence was presented to the media that seemed to show that Merck was aware of the health risks associated with Vioxx. An indictment of Merck could occur if it is found that the company knew of the cardiovascular risks and yet obscured the dangers in an effort to market and sell the drug. Specifically, the Department of Justice will investigate whether “Merck mislead regulators or

¹²⁶ *Big Health Plan Suspends Use of Painkiller*. Gardiner Harris. New York Times. January 29, 2005.

¹²⁷ It is also worth noting that at this same time, Merck lost its patent protection for its very popular drug Fosamax, used for bone-replacement. The decision took away the patent ten years earlier than expected. It was thought that Fosamax could soften the effect of the loss of Vioxx. The loss of the Fosamax patent only added to Merck’s problems at this time.

¹²⁸ “Vioxx, Celebrex, and Bextra: Recall News.” Ibid.

perhaps caused federal health programs to pay for the prescription drug when its use was not warranted.”¹²⁹

Like the SEC investigation, the Department of Justice probe into Merck’s handling of Vioxx is still pending.

Congressional Investigation

Merck’s voluntary recall of Vioxx captured the attention of not just the Securities and Exchange Commission and the Department of Justice but also the United State Congress. Both the Senate Finance Committee and the House Committee on Government Reform held hearings to examine the actions of Merck and the FDA regarding Vioxx. This paper will begin with an examination of the findings of the Senate hearing.

On November 18, 2004 the Senate Finance Committee chaired by Republican Senator Charles Grassley of Iowa, heard testimony from witnesses in an effort to sort through the ill fated story of Vioxx. In his opening statements to the Committee, Sen. Grassley stated that the purpose of the hearing was to ensure that Congress was performing its function as overseer of both the federal bureaucracy and the private sector.¹³⁰ He noted that the Committee would consider the decisions and action of both the FDA and Merck Pharmaceuticals in its inquiry and investigation.¹³¹ And while Sen. Grassley stated that both the FDA and Merck have a history of good standing in regards to their business practices, the Iowa Senator had harsh comments for both organizations in his opening remarks. He stated, “We’ll see that the FDA failed to heed the words of even its own scientists [spelling changed]. It also looks like the FDA allowed itself to be manipulated by Merck on labeling changes that became necessary after a review by Merck that’s known as the VIGOR trial... Now, over a period of 22 months, Merck aggressively marketed Vioxx knowing that

¹²⁹ “The Progress Report.” <http://www.americanprogressaction.org/site/pp.asp?c=k1LWJcP7H&b=246453>

¹³⁰ “U.S. SENATOR CHARLES E. GRASSLEY (R-IA) HOLDS HEARING ON FDA, MERCK AND VIOXX: PUTTING PATIENT SAFETY FIRST.” Congressional Quarterly Transcriptions. November 18, 2004.

¹³¹ Ibid.

consumers and doctors were largely unaware of the cardiovascular risks in the VIGOR trial.”¹³² Senator Grassley clearly believed that both parties should receive some blame.

On the day of the hearing, the Committee heard testimony from three panels of witnesses. The first panel included Dr. David Graham, Dr. Gurkirpal Singh, and Dr. Bruce Psaty. Dr. David Graham testified first. Dr. Graham’s testimony was a scathing attack of the Food and Drug Administration, his employer for over twenty years. He testified that the FDA completely failed in its duty to serve as overseer of the prescription drugs which enter the market. He called the actions of the FDA in regards to Vioxx a “profound regulatory failure.”¹³³ He stated that prior to the submission of Vioxx to the FDA, Study 090 performed by Merck, showed a seven-fold increase in the number of heart attacks in patients receiving Vioxx. At the time of approval, however, the FDA did not include that fact on Vioxx labeling.¹³⁴ He then noted that it was not until eighteen months after the VIGOR study results were published that the FDA made a labeling change to Vioxx.¹³⁵ Dr. Graham went on to say that because of the way that the FDA is currently organized, citizens of the United States would be “virtually defenseless” if another medication is proved to be dangerous after it receives FDA approval.¹³⁶ He noted that the Office of New Drugs, which is higher in the FDA hierarchy than Graham’s office of Drug Safety, is very reluctant to issue new regulations for drugs already on the market. This is because the same organization that is responsible for approving the drug is also responsible for making the decision to pull the drug from the market. As Dr. Graham stated, that is “an inherent conflict of interest.”¹³⁷ In Dr. Graham’s estimate, somewhere between 88,000 and 133,000 Americans suffered heart attacks or strokes as a result of using Vioxx and somewhere between 30% and 40% died from those incidences.¹³⁸ To make this figure crystal clear in the minds of the Senate Committee, Dr.

¹³²Ibid.

¹³³Ibid.

¹³⁴Ibid.

¹³⁵Senate Finance Committee Transcript. November 18, 2004. Ibid.

¹³⁶Ibid.

¹³⁷Ibid.

¹³⁸Ibid.

Graham illustrated his point by stating that the number of Americans adversely affected by Vioxx is the equivalent of between 500 and 900 passenger aircrafts falling from the sky.¹³⁹

Dr. Graham testified that after he concluded his study in the summer of 2004, the study which was published in the *Lancet*, he was “pressured to change [my] conclusions and recommendations.”¹⁴⁰ He presented an email from the director of the OND which supported that testimony. The comments of Dr. Graham were dramatic and forceful and they sent shockwaves across the government and the drug industry.

Following the comments of Dr. David Graham, Dr. Bruce Psaty testified. Dr. Psaty, a cardiovascular disease epidemiologist at the University of Washington in Seattle, focused his testimony on the development and extent of Merck’s knowledge regarding the cardiovascular risks of Vioxx.¹⁴¹ Dr. Psaty also delivered harsh criticism of the FDA’s handling of the Vioxx approval and post-market observation. He noted that at the time Vioxx was presented to the FDA for review and approval, only 371 patients had received 25mg doses of Vioxx for one year or more.¹⁴² He stated that in his opinion, that was far too few patients to adequately evaluate the effects of the drug. Like Dr. Graham, he also pointed out that there was over a one year delay between the time when the FDA received and reviewed the result of the VIGOR trial and when they made a label change. Dr. Psaty cited various statistics and findings from the previously mentioned studies such as VIGOR and APPROVe. He stated that, in his medical judgment, there is a strong argument that the gastrointestinal benefits which would arguably be received by taking Vioxx over other traditional

¹³⁹Ibid.

¹⁴⁰Ibid.

¹⁴¹Dr. Psaty is widely known for his integrity. The Seattle Times wrote an article about him in which they noted that Dr. Psaty angered his medical professors when he refused to kill and dissect a dog and he is frequently ostracized by his fellow doctors because he refuses to attend banquets paid for by drug companies. http://seattletimes.nsource.com/html/localnews/2002130815_psaty26m.html. He is, evidently, held in the highest regard by the public.

¹⁴²Senate Finance Committee Transcript. November 18, 2004. Ibid.

NSAIDS would not outweigh the costly cardiovascular risks now associated with the drug.¹⁴³ He noted that while gastrointestinal problems can be serious they are rarely life threatening, whereas 25% of heart attacks are deadly.¹⁴⁴ He concluded his remarks with suggested reforms that might ensure another incident like this never occurs. Among these reforms were the requirement of large and long-term studies of every drug and the creation of an independent center for drug safety to evaluate drugs after they enter the market; a suggestion which echoed Dr. Graham's conclusion that the FDA, as it is currently arranged cannot both approve and monitor drugs.¹⁴⁵

Following the comments of Dr. Psaty, the Senate Committee heard the testimony of Dr. Singh. Dr. Singh made very similar comments to those made by the two doctors preceding him. However, he focused his attention more on the actions of Merck. He testified that he has devoted much of his career to lecturing physicians on the latest drugs to enter the market place.¹⁴⁶ To that end, he often contacts drug manufacturers to secure information regarding safety data. While Merck had always responded to his requests "promptly and in a scientific fashion," when he questioned the company about the VIGOR results he did not receive that same treatment. Dr. Singh testified that after he persisted in his inquiries regarding VIGOR, he was warned by Merck that if he continued to bother the company for information there would be "serious consequences."¹⁴⁷

Dr. Singh commented that Merck clearly believed that the gastrointestinal benefits of Vioxx were important enough and valuable enough to the drug market to continue regardless of any associated cardiovascular consequences. He went on to say, however, that, "the trade-off of heart attacks for the rare instances of

¹⁴³Ibid.

¹⁴⁴Ibid.

¹⁴⁵Ibid.

¹⁴⁶Ibid.

¹⁴⁷Ibid.

stomach bleeds is not a reasonable one.”¹⁴⁸ He stated, like Dr. Psaty that there were no large studies to either prove or disprove the link between Vioxx and cardiovascular events. And he opined that the decision to not carry out those large studies was for marketing and public relations reasons.¹⁴⁹ He concluded his comments with ways to reform the drug review and approval system, again to include the creation of an independent drug safety office.

After the testimony of panel one, Dr. Sandra Kweder offered a defense of the FDA as acting director of the Office of New Drugs. In her defense of the FDA, Dr. Kweder contended that the FDA’s Arthritis Committee extensively reviewed the information presented to it regarding Vioxx. According to her testimony, the FDA was aware of some limited data that suggested the *potential* for cardiovascular risk. However, it was the gastrointestinal benefits that made the drug appealing to the FDA at the time of approval.¹⁵⁰

After approval, when the FDA received the results of the VIGOR trial, Dr. Kweder asserted that the FDA “worked actively and vigorously with Merck to inform public health professionals of what was known regarding [cardiovascular] risk with Vioxx, and to pursue further definitive investigations to better define and quantify this risk.”¹⁵¹ She also stated her objection to the testimony of Dr. Graham by claiming that Dr. Graham’s estimates of Vioxx’s toll were mere mathematical guesses and “not real deaths.”¹⁵² She went on to say that the FDA about which Dr. Graham spoke is not the FDA that she knows.¹⁵³ She stated that it was the FDA’s vigilant demand that Merck hold long term trials after the initial approval that led to the studies which directly resulted in Merck’s withdrawal of Vioxx. And while she did not fully endorse the widely recommended independent Office of Drug Safety, she did say it was an idea “worth looking at.”¹⁵⁴

¹⁴⁸Ibid.

¹⁴⁹Ibid.

¹⁵⁰Ibid.

¹⁵¹Statement of Sandra Kweder, MD. November 18, 2004. <http://www.fda.gov/ola/2004/vioxx1118.html>.

¹⁵²Senate Finance Committee Transcript. November 18, 2004. Ibid.

¹⁵³Ibid.

¹⁵⁴Ibid.

Finally, the November 18, 2004 Senate Hearing concluded with a defense of Merck Pharmaceuticals in testimony from Merck's CEO and President Raymond Gilmartin. Mr. Gilmartin began his remarks with comments regarding the unique quality of Vioxx. He noted that Vioxx was the only NSAID that could provide acute pain relief without the gastrointestinal side effects that accompanied similar drugs. Mr. Gilmartin made the claim that at the time Merck presented the drug to the FDA for approval Merck researchers had "extensively studied the medicine and found it to be safe and effective."¹⁵⁵ He specifically denied that evidence prior to the approval showed any elevation in the risk of cardiovascular events. He commented on the VIGOR study and defended Merck's analysis of the study which led to the conclusion that the difference in cardiovascular event rates was due to the preventative effect of naproxen. He concluded his remarks by proclaiming his confidence that after a thorough investigation of Merck's conduct it will be found that the company acted in a manner consistent with its main goal of patient safety.¹⁵⁶

The United States House of Representatives conducted its own investigation on the Vioxx matter. The May 5, 2005 hearing before the Committee on Government Reform covered much of the same topics as the Senate hearing the year prior. However, the House committee hearing focused on the issue of Merck's aggressive advertising maneuvers. The committee examined over 20,000 pages of internal Merck documents which offered tremendous insight into the techniques used by Merck's sales representatives in selling Vioxx to physicians.

¹⁵⁵Senate Finance Committee Transcript. November 18, 2004. Ibid.

¹⁵⁶Ibid.

The internal documents showed that Merck's sales staff was taught how to sell Vioxx to physicians without mentioning the cardiovascular risks associated with the drug.¹⁵⁷ If physicians inquired about the cardiovascular risks, sales representatives were instructed to refer to a "Cardiovascular Card" when making presentations.¹⁵⁸ The card was created in April of 2000, one month after the VIGOR study was completed. It contained information from studies which had previously been submitted to the FDA but did not include any data or statistics from the VIGOR study which showed an increase risk of heart attack in patients taking Vioxx. And although the FDA Arthritis Committee voted in 2001 to require Merck to notify physicians of the VIGOR study findings, a subsequent Merck memorandum sent to all sales associates clearly ignored the orders of the FDA. The memo instructed sales representatives to respond to any questions about the VIGOR study by saying, "I cannot discuss the study with you."¹⁵⁹

The sales team was given extensive and sometimes bizarre training and instruction regarding the manner in which they sold or "detailed" Vioxx to physicians. They were trained how to smile, speak, and position themselves in the most effective manner when talking with doctors.¹⁶⁰ They were also told to use Dr. Martin Luther King Jr.'s "I Have a Dream Speech" to help sell Vioxx. Representative Elijah Cummings of Maryland read from the Merck training manual during the hearings. The manual stated, "[Dr.] King was someone with goal-focus – he kept getting shut down but kept going.... Just as with a physician, you must keep repeating the compelling message and at some point, the physician will be 'free at last' when he or she prescribes the Merck drug, if that is most appropriate for the patient."¹⁶¹ The sales force was taught how to capitalize on every interaction with a physician in order to sell Merck pharmaceuticals including Vioxx.

Representative Henry Waxman of California stated in the committee report that it was clear from the Merck

¹⁵⁷"Merck CEO Resigns as Drug Probe Continues." May 6, 2005. Washington Post. <http://www.washingtonpost.com/wp-dyn/content/article/2005/05/05/AR2005050501115.html>

¹⁵⁸Ibid.

¹⁵⁹Ibid.

¹⁶⁰Ibid.

¹⁶¹Ibid.

documents that the goal of the company was sales and not education.¹⁶²

Steven Galson, director of the FDA's Center for Drug Evaluation and Research testified that the FDA was unaware of the details of Merck's advertising campaign.¹⁶³ However, he stated that Merck's legal obligations require them only to provide the information that was approved in drug labeling. He went on to say that the promotional materials used by the Merck sales team were "accurate based on the [Vioxx] label."¹⁶⁴ Mr. Galson did state that Merck needed to convey only truthful information to physicians when selling Vioxx and based on the internal documents and memos it appeared to him that Merck had not given doctors "the entire picture."¹⁶⁵

Dennis Erb, Merck's Vice President testified on behalf of Merck. He testified that Merck acted appropriately throughout the Vioxx situation. He stated that the sale's staff was trained to be "accurate and balanced" in presenting drug information to physicians.¹⁶⁶ Erb's defense of Merck's decision not to tell doctors about the cardiovascular risks associated with Vioxx was based on the fact that Merck believed that naproxen, the control drug in earlier studies, decreased the risk of heart attack as opposed to Vioxx increasing the risk. He went on to note that Merck was considering approaching the FDA about reapplying for market approval of the drug.

Committee chairman, Representative Tom Davis of Virginia, was slow to criticize Merck, unlike his Senate

¹⁶²"Congressional Hearing Focuses on Merck's Marketing for COX-2 Drug Vioxx" Medical News Today. May 7, 2005. <http://www.medicalnewstoday.com/medicalnews.php?newsid=23978>

¹⁶³Ibid.

¹⁶⁴Ibid.

¹⁶⁵Ibid.

¹⁶⁶Merck CEO Resigns as Drug Probe Continues." May 6, 2005. Washington Post. Ibid.

counterpart Charles Grassley. Davis stated that while the internal documents raised some questions he was not prepared to criticize the company without further information and evidence. He commented that a “wide-awake physician” would have known about the heart risks associated with Vioxx by reading the now famous editorials about the drug in various medical journals and newspapers. Another witness to appear before the committee, however, Dr. Michael Wilkes, refuted that statement by Chairman Davis. Dr. Wilkes, vice dean for medical education at the University of California-Davis, commented that doctors are often too busy with patients to read such medical literature. Instead, they rely on the information provided to them by the pharmaceutical salesmen.¹⁶⁷

As a side note to the hearings, on the same day as the House committee’s hearing, Merck CEO Raymond Gilmartin abruptly resigned his position. Gilmartin held the position of CEO for over eleven years and was only ten months away from retirement. The Washington Post reported that until the Vioxx debacle, Gilmartin was held in high regard in the pharmaceutical industry.¹⁶⁸ Since the September 2004 withdrawal and the subsequent investigations and hearings, the reputation of Merck and Gilmartin plummeted. Gilmartin was replaced by Richard Clark, the long time president of Merck’s manufacturing division.

The hearings held in both the Senate and the House of Representatives are a vital part of the Vioxx story. The story of the failed drug is a complicated one and the hearings helped to map out the elements of each stage of the drug’s life. Through witness testimony and congressional comments, the details of Merck’s pre-approval research were fleshed out, the process of the FDA’s review and approval were discussed, the post-approval

¹⁶⁷“Selling Vioxx: Merck used code-named projects to boost sales despite safety concerns.” May 5, 2005. The Seattle Times.

¹⁶⁸*Ibid.*

of the drug was better understood, the intricacies of Merck's marketing strategy were discovered, and the situation surrounding the voluntary withdrawal of the drug were explained. Additionally, the fact that the Congress took the time to review and examine the exact happenings of the Vioxx debacle clearly indicated that there was a problem and some party should shoulder the responsibility for causing that problem. The congressional duty of oversight is one that is not taken lightly. Congress' interest in Vioxx sent a strong message that irresponsible actions which jeopardize public safety on the part of either the pharmaceutical company or the FDA would not be tolerated.

The congressional hearings also brought critical public attention to the story. While the voluntary withdrawal of Vioxx created some awareness, congressional participation into the investigation gave a fully developed glimpse of the situation. Given that there were tens of millions of people prescribed Vioxx, the issue was a sensitive one for a large number of Americans.

The most important consequence of the congressional hearings, however, was the litany of court cases that immediately followed. Many legal analysts viewed the hearings as a sort of "dress rehearsal" for the thousands of Vioxx cases that overwhelmed the justice system. The testimony offered at the hearings provided insight into the types of arguments to be made by plaintiffs as well as Merck in future cases.

Vioxx Litigation

The voluntary recall of Vioxx by Merck and the congressional investigations which followed led to a flood of lawsuits in both state and federal courts. The immense popularity of Vioxx which brought Merck billions of dollars in profits has worked against the pharmaceutical giant in the post-market litigation phase. The

twenty million people who took the arthritis medication are now all potential plaintiffs.¹⁶⁹ Every day the company is faced with new law suits from across the country. The future of Merck depends largely on the company's ability to contend with its ever growing court docket. Merck is not the first company to pull a product from the market and then suffer the litigation consequences. Merrell Dow Pharmaceuticals pulled its Bendectin, a morning sickness drug from the market in 1983, after it had been used by over ten million pregnant women. A similar situation was faced by Dow Corning Company when it was forced to remove its silicone breast implants from the market in 1992.¹⁷⁰ And while Merck is not the first company to chart these rough waters, their course of action is up in the air.

Thus far, four Vioxx cases have been decided. Three of those cases have been state court cases and one case was decided in federal court. Some analysts argue that Merck will fair best in federal court. Others disagree. To fully understand the current state of litigation and whether the plaintiffs have the edge or whether Merck is on top, it is best to examine the four cases which have already been tried. Each case brought new facts and new arguments and each sheds light on the current state of the Vioxx litigation.

Ernst v. Merck

The first case to be heard in state court was *Ernst v. Merck*. The facts of the *Ernst* case were already discussed in detail in the introduction to this paper. Robert Ernst was a physically active man who died of a cardiac arrhythmia and atherosclerosis. He had been taking Vioxx for seven months. His wife, Carol Ernst filed her suit against Merck in Texas's 23rd District Court in 2002. She alleged negligent failure to warn of the dangers associated with the drug and civil conspiracy to conceal that danger.¹⁷¹

Legal analysts believed the *Ernst* case to be a favorable one for Merck. Because the case was filed in state

¹⁶⁹ "No Easy Prescription for Vioxx Litigation." Eriq Gardner. Law.com. www.law.com/jsp.artcile.jsp?id=1100535366555.

¹⁷⁰ Ibid.

¹⁷¹ Jacqueline G. Cohen. *Recent Developments in Health Law: Merck and the Vioxx Decision: Playing by the Changing Rules of the Chemical Exposure Game*. 2005 American Society of Law, Medicine & Ethics Journal of Law. Winter, 2005. 33 J.L. Med. & Ethics 866.

court, Merck would have the benefit of state law limitations on financial liability.¹⁷² Texas law has a cap on punitive damages that does not allow damages to exceed twice the amount rewarded for economic damages. Also, because Carol and Robert Ernst had been married less than a year when he died, non-economic damages it was thought would be small. Additionally, Robert Ernst did not suffer a prolonged illness, so economic damages would also likely be relatively miniscule. The most important advantage the Merck team believed it had going into the *Ernst* case, however, was the lack of scientific causation evidence.¹⁷³

Prior to the beginning of the trial, Kent Jarrell, a spokesperson for Hughes, Hubbard, and Reed, one of the law firms representing Merck, commented on the defense team's position in the case. He stated, "This is not a normal Vioxx case, which is about heart attacks and strokes being increased by the use of the drug... [The plaintiff] is going to make this about the behavior of the company. We plan on making it about the specifics of causation."¹⁷⁴ Robert Ernst died of cardiac arrhythmia and Merck claimed that no reliable scientific evidence had found that Vioxx caused that.¹⁷⁵ In their motion for summary judgment, the defense argued that the plaintiffs must "establish to a reasonable degree of medical certainty" that Vioxx probably caused Mr. Ernst's fatal cardiac arrhythmia.¹⁷⁶ That motion was overruled by the Texas judge.

In a case in which the plaintiff alleges injury due to exposure to a harmful drug as in *Ernst*, the plaintiff bears the burden of proof in meeting the causation requirement. The plaintiff must show that he was 1- exposed to the drug, 2- the drug is capable of causing his injuries (general causation), 3- the exposure caused his injuries (specific causation), and 4- the defendant was responsible for the exposure that caused the injury.¹⁷⁷ In order to prove general causation, scientific evidence is presented. In order to prove specific causation, scientific and statistical evidence and testimony are offered.

¹⁷²Ibid.

¹⁷³Ibid.

¹⁷⁴"How a Small-Firm Attorney Took on Merck and Won." *Texas Lawyer*, August 30, 2005.

¹⁷⁵Jacqueline G. Cohen. *Recent Developments in Health Law: Merck and the Vioxx Decision: Playing by the Changing Rules of the Chemical Exposure Game*. Ibid.

¹⁷⁶Ibid.

¹⁷⁷These requirements are found in the Restatement (Third) of Torts, Section 28. The comments offered in this section explain that pharmaceutical drugs fall under the toxic substance reference made in Section 28.

The defense likely would have had a solid opportunity to win on the issue of causation but the plaintiff's legal team did not put on a causation case.¹⁷⁸ And the jury that heard the *Ernst* case clearly found that proof of causation was not necessary.¹⁷⁹ Plaintiff lead attorney Mark Lanier commented before trial, "I win the case whether it is a heart attack or an arrhythmia. Merck internally knew that Vioxx caused both. Merck knew it before it sold its first pill. I don't have to use outside experts. I will use Merck's own documents, their own emails, their own scientists."¹⁸⁰ The plaintiff's strategy was to prove Merck to be an irresponsible company that marketed a dangerous product. It seemed that the plaintiff's legal team didn't care about scientific evidence at all. When asked about the data that suggested Vioxx to be dangerous only after eighteen months of use, Lanier stated, "That's just bogus. Vioxx can kill you after 18 months; it can kill you after six weeks."¹⁸¹ The defense wanted the case to be judged on its science. The plaintiffs wanted it to be about the bad conduct of Merck. The jury sided with the plaintiffs.

The jury awarded Ernst \$253.4 million in damages. Of that award, \$229 was punitive. Plaintiffs had only asked for \$40 million. Merck has appealed the ruling. General Counsel for the company argued that the jury in the *Ernst* case was permitted to hear irrelevant evidence that was not based on science.¹⁸² The legal team also argued that the plaintiffs did not "meet the standard set by Texas law to prove Vioxx caused Mr. Ernst's death."¹⁸³

¹⁷⁸Ibid.

¹⁷⁹Jacqueline G. Cohen. Recent Developments in Health Law: Merck and the Vioxx Decision: Playing by the Changing Rules of the Chemical Exposure Game. Ibid

¹⁸⁰How a Small-Firm Attorney Took on Merck and Won." Texas Lawyer, August 30, 2005. Ibid.

¹⁸¹Ibid.

¹⁸²Jacqueline G. Cohen. Recent Developments in Health Law: Merck and the Vioxx Decision: Playing by the Changing Rules of the Chemical Exposure Game. Ibid.

¹⁸³Kevin McCoy, Merck to Face First Vioxx Trial Before Texas Jury Next Month, USA Today. June 29, 2005. Ibid.

The *Ernst* case is not binding precedent for cases in other state courts. However, the *Ernst* decision has clearly shaped the legal battle that has ensued following the August 2005 decision. The Merck legal team has moved forward with a better understanding of the importance of defending the company's actions and reputation as opposed to focusing solely on causation. The plaintiff's attorneys have vigorously pursued the jurors in the case to get a better sense of the impressions they had of the case and the arguments presented.¹⁸⁴ *Ernst v. Merck* was a clear victory for the plaintiffs and a major set back for Merck. However, with thousands of cases yet to be tried and with a legal team eager to learn from their mistakes, Merck's fate was hardly sealed by the *Ernst* defeat.

Humeston v. Merck

Frederick Humeston of Boise, Idaho suffered a heart attack in 2001 at age 56. Humeston, a twice wounded Vietnam, Marine Corps Veteran and postal worker, alleged that Vioxx was to blame for his heart attack.¹⁸⁵ He began taking Vioxx as a painkiller after an injury to his right knee.¹⁸⁶ He continued to take the drug when he discovered that it eased the pain in his left knee which had been wounded by shrapnel in Vietnam and troubled him ever since.¹⁸⁷ He only took Vioxx intermittently from May until September of 2001.¹⁸⁸ Humeston claimed in his suit against Merck that taking Vioxx caused a blood clot that led to his heart attack. The *Humeston* case began on September 12, 2005, prior to the decision in *Ernst v. Merck*, and it was the first of 2,300 Vioxx cases to be filed jointly in New Jersey Superior Court. Like many of the other plaintiffs, Humeston, an Idaho resident, brought his case to New Jersey because Merck is based out of

¹⁸⁴Jacqueline G. Cohen. Recent Developments in Health Law: Merck and the Vioxx Decision: Playing by the Changing Rules of the Chemical Exposure Game. Ibid.

¹⁸⁵"Merck Faces Big Vioxx Showdown in New Jersey. August 12, 2005. <http://money.cnn.com/2005/08/12/news/fortune500/vioxx/>

¹⁸⁶Ibid.

¹⁸⁷Ibid.

¹⁸⁸Lisa Brennan. Keen Questioning by Jurors Demystifies Vioxx Trial. New Jersey Law Journal. October 3, 2005.

Whitehouse Station, New Jersey.

The *Humeston* case ended up being a slam dunk victory for Merck. Legal analysts believe that Merck's success in this second state court case had more to do with jury selection and a less sympathetic plaintiff than it did with legal strategy and evidence.¹⁸⁹ The jurors were primarily white middle-class people. The jury included a teacher, county prosecutor, bank executive, bookkeeper, accountant, and real estate broker.¹⁹⁰ These jurors played an important role in this case, not just in the post-trial deliberation but also in their role as fact finder due to the allowance of jury questions. Few courts allow juror questions. Judge Carol Higbee, however, who is presiding over the jointly filed Vioxx cases, has made it a practice ever since New Jersey judges were given the authority to allow such questions in 2002.¹⁹¹ The juror questions in *Humeston* were foreshadowing of the final outcome.

The questions posited by the jurors made it immediately clear that they were less concerned with Merck's actions and more concerned with whether or not something other than Vioxx led to Humeston's blood clot and heart attack. The questions also assured the court that the jurors had focused intently on the evidence presented. The jurors showered Humeston with questions. They asked him if he ever combined Vioxx with narcotics.¹⁹² He was asked if he ever discussed the side effects of the drug with his doctors.¹⁹³ Jurors asked Humeston if the events of September 11th had caused him stress.¹⁹⁴ The questions from the jurors came

¹⁸⁹Lisa Brennan. *Vioxx Verdict Postmortem: Weak Case, Tough Jury*. New Jersey Law Journal. November 7, 2005.

¹⁹⁰Ibid.

¹⁹¹Lisa Brennan. *Keen Questioning by Jurors Demystifies Vioxx Trial*. New Jersey Law Journal. October 3, 2005. Ibid.

¹⁹²Ibid.

¹⁹³Ibid.

¹⁹⁴Ibid.

after a long and trying day in which Humeston testified to the effect of his heart attack on his quality of life. His testimony was emotional and heart felt but the questions from the jurors made clear that they had very little sympathy. That sentiment on the part of the jury was evident again when they came to a verdict in favor of Merck.

Legally, the *Humeston* case was distinguishable from the *Ernst* case in that the lawyers for the plaintiffs focused on the science of the case. The decision by lead plaintiff attorney, Christopher Seeger, to place emphasis on the scientific issues was viewed by many observers to be a costly error.¹⁹⁵ Instead, a wiser path for Seeger might have been to have followed the example set in the *Ernst* case and honed the jury's attention on the marketing practices of Merck. Additionally, the plaintiff's team was challenged when Judge Higbee allowed the admission of portions of a memo by two Food and Drug Administration officials which concluded that short-term use of Vioxx caused no greater cardiovascular risk than everyday pain killers.¹⁹⁶ The memo only strengthened the scientific case put forward by the defense. Attorney, Mark Lanier, who successfully tried the *Ernst* case commented after the decision in *Humeston* that it is "hard to try a case on the science."¹⁹⁷ Lanier went on to note that *Humeston* was only the second jury trial Seeger had ever tried.¹⁹⁸

In the end, the jury deliberated for eight hours and found 8-1 that Merck had properly alerted prescribing doctors to the link between Vioxx and increased risk of heart attacks. The only juror to rule against Merck on

¹⁹⁵Lisa Brennan. *Vioxx Verdict Postmortem: Weak Case, Tough Jury*. New Jersey Law Journal. November 7, 2005. Ibid.

¹⁹⁶Ibid.

¹⁹⁷Ibid.

¹⁹⁸Ibid.

the failure to warn issue was the only minority on the jury.¹⁹⁹ The verdict in favor of Merck was important for several reasons. The verdict was likely to deter some cases involving short-term users of Vioxx.²⁰⁰ Because the majority of the science concludes that the greatest risk of cardiovascular events occurred in patients taking Vioxx for eighteen months or longer, plaintiffs such as Humeston who took the drug for only a few months, are at a disadvantage. The victory for Merck was also immediately felt on Wall Street. Merck shares rose six percent after the *Humeston* case.²⁰¹ Also, the concern over possible collateral estoppel on the failure to warn issue was eliminated with the Merck victory the case. Had the jury found for the plaintiffs on the failure to warn issue, Merck could have been precluded from retrying the issue in the other New Jersey Superior Court cases.²⁰² And most importantly, the verdict for Merck gave the pharmaceutical company back some of the momentum it had lost after the *Ernst* defeat. The score card was tied up between the plaintiffs and the defendants. The following case was in federal court and it broke the tie.

Plunkett v. Merck

In February of 2005, a seven judge panel consolidated hundreds of individual and class-action lawsuits filed in federal courts against Merck. The cases were consolidated in a federal court in New Orleans before Judge Eldon E. Fallon, a judge well liked by the plaintiffs' lawyers.²⁰³ In the consolidation order from the administrative panel, it was stated that the assignment went to Judge Fallon because he had both the time and the experience needed to fulfill the duty.²⁰⁴ Just the year before, Judge Fallon had presided over all the federal injury claims which stemmed from the Propulsid litigation. Propulsid was a heartburn medication

¹⁹⁹Ibid.

²⁰⁰Lisa Brennan. *Merck found not liable for Vioxx user's heart attack*. New Jersey Law Journal. November 4, 2005.

²⁰¹Ibid.

²⁰²Ibid.

²⁰³"Federal Panel Consolidates Vioxx Suits." New York Times. February 17, 2005.

²⁰⁴Ibid.

that was linked to eighty deaths and over 100 heart attacks before it was removed from the market in 2000.²⁰⁵ Given his oversight of that expansive litigation, Judge Fallon was viewed by the panel as strong choice. It should be noted that due to Hurricane Katrina's toll on the city of New Orleans, Judge Fallon's court was moved temporarily to Houston, Texas. So once again, Merck found itself in a Texas courtroom.

Many analysts believe that the upper hand in federal court belongs to Merck. The reason for this upper hand is due in large part to the federal rules involving scientific evidence. The 1993 Supreme Court decision in *William Daubert v. Merrell Dow Pharmaceuticals* created a two part test for admitting scientific evidence in federal cases. In order to be admitted scientific testimony must, 1- convey scientific knowledge and 2- it must be relevant.²⁰⁶ The Supreme Court explained "scientific knowledge" to mean knowledge that is grounded in methods and procedures of science that is more than just subjective speculation.²⁰⁷ Under *Daubert* federal judges are charged as "gatekeepers" and are given the authority to determine what scientific evidence can be presented in drug and medical device tort cases.²⁰⁸ Federal judges must examine scientific evidence and ultimately admit only that evidence that meets the two pronged *Daubert* test. This is important for Merck particularly in cases of short-term Vioxx use (eighteen months or less) where the strongest scientific evidence is believed to be on Merck's side. Therefore, many legal analysts believe that Merck would be well served to move as many state actions to the federal level as possible.²⁰⁹ The *Plunkett* case was the first case to be tried in federal court and it was decided in Merck's favor.

²⁰⁵Ibid.

²⁰⁶Jacqueline G. Cohen. Recent Developments in Health Law: Merck and the Vioxx Decision: Playing by the Changing Rules of the Chemical Exposure Game. Ibid.

²⁰⁷*Daubert v. Merrell Dow Pharmaceuticals, Inc.* 113 S. Ct. at 2796.

²⁰⁸"No Easy Prescription for Vioxx Litigation." Eriq Gardner. Law.com. www.law.com/jsp.artcile.jsp?id=1100535366555.

²⁰⁹Ibid.

The *Plunkett* case began in December of 2005. The plaintiff, Evelyn Irvin Plunkett was married to Richard Irvin. Richard Irvin approached his physician in April 2001 with complaints of back strain he suffered while working for a seafood wholesaler in St. Augustine, Florida.²¹⁰ His doctor prescribed Vioxx for the pain. One month later, Irvin was found by his co-workers dead at his desk, having suffered a heart attack.²¹¹ His widow claimed her husband was in excellent health. However, autopsy reports found that Irvin had moderate to severely clogged arteries.²¹² The autopsy also showed a blood clot in a major coronary artery which caused an irregular heartbeat. Evelyn Plunkett claimed that the blood clot was caused by her husband's Vioxx use.²¹³

The *Plunkett* case lasted only two weeks before it went to the jury.²¹⁴ On December 12, 2005, after four days of deliberations, Judge Fallon declared a mistrial.²¹⁵ The jury was unable to decide whether Merck was liable for the death of Richard Irvin and whether the company failed to issue safety warnings regarding Vioxx's potential cardiovascular risks.²¹⁶ The case was rescheduled for February 2006.

The second *Plunkett* case was heard in the originally selected New Orleans Federal Court room and it ended in a critical victory for Merck. The trial again lasted approximately two weeks and hinged on the short

²¹⁰"Merck faces first hearing on Vioxx as lawsuits mount." November 17, 2004. [www.usatoday.com.
http://www.usatoday.com/money/industries/health/drugs/2004-11-17-merck-vioxx-hearing-lawsuits_x.htm](http://www.usatoday.com/money/industries/health/drugs/2004-11-17-merck-vioxx-hearing-lawsuits_x.htm)

²¹¹Ibid.

²¹²"First Vioxx federal trial to focus on length of use." November 26, 2005. <http://www.thetimesonline.com/articles/2005/11/26/business/business/4f448fed29275ecc862570c400602f02.txt>

²¹³Ibid.

²¹⁴On the first day of jury deliberations, The New England Journal of Medicine published "Expression of Concern" article mentioned previously regarding the 2000 VIGOR study. So that publication served as a backdrop for the federal jury deliberations but it is thought that the article had no play on the jury being unable to reach a verdict.

²¹⁵Brenda Sapino Jeffreys. "Mistrial Declared in First Federal Vioxx Case." December 13, 2005. The Legal Intelligencer.

²¹⁶Ibid.

period of time Evelyn Plunkett's husband, Richard Irvin took Vioxx. The plaintiff's legal team argued that it was Vioxx's enzyme blocking capability which even after only a few weeks of use led to the blood clot. Merck's defense defeated that argument. Legal analysts believe that Merck was given the advantage in *Plunkett* after Judge Fallon ruled that two of the plaintiff's chief experts, a cardiologist and a pathologist, would not be allowed to testify that Vioxx was to blame for Irvin's heart attack.²¹⁷ The judge decided that while the doctors were experts in their respective fields, they were not experts on Vioxx.²¹⁸ The ruling was a clear indication that Judge Fallon would strictly observe his gatekeeper role under *Daubert*. It seems that the bottom line in the *Plunkett* case was that heart attacks are common and it will require a lot of strong scientific evidence to prove that Vioxx caused a particular heart attack. A lawyer for Merck commented after the *Plunkett* trial that the jury had found, "Merck scientists lived up to their legal and ethical responsibilities when manufacturing and marketing Vioxx."²¹⁹ The jury deliberated for three hours and forty minutes, the shortest time of any of the previous trials.

The victory in *Plunkett* case was another boost for the Merck legal team. Again, the case served as a deterrent to plaintiffs considering bringing claims against Merck involving only short term Vioxx use. The win for Merck could also serve the company well if there is a future settlement of the federal cases consolidated under Judge Fallon.²²⁰ And importantly, the *Plunkett* case was the first tried in federal court and the victory for Merck, in many ways set the tone for future federal court cases.

Cona/McDarby v. Merck

²¹⁷ "Merck cleared in first federal Vioxx case." February 17, 2006. <http://www.healthyskepticism.org/library/ref.php?id=4291>.

²¹⁸ Ibid.

²¹⁹ Ibid.

²²⁰ "Jury rules in favor of Merck in Vioxx case." February 17, 2006. MSNBC.com. <http://www.msnbc.msn.com/id/11408785/>

The next case, and the most recently decided case, brought Merck back to state court in New Jersey. *Cona/McDarby* involved the claims of two plaintiffs whose cases were combined into one by Judge Carol Higbee. Merck strongly protested the combining of the plaintiffs' claims and urged the judge to hear each case on its own merits.²²¹ Plaintiffs' attorneys favored the consolidation because it would allow for more cases to be heard sooner.²²² Judge Higbee grouped Cona's and McDarby's claims because they were similar in facts and length of time each plaintiff took Vioxx.²²³ Unlike the previous New Jersey case, both plaintiffs claimed to have taken Vioxx for over eighteen months. The jury in the case split the verdict rejecting the claim of one plaintiff and awarding compensation to the other.

John McDarby, a seventy-seven year old from Park Ridge, New Jersey suffered a heart attack in his living room and broke his hip as a result.²²⁴ McDarby is now confined to a wheelchair. He claimed to have taken Vioxx for four years prior to his heart attack. Thomas Cona, sixty years old from Cherry Hill, New Jersey, was a business man and was struck down by a heart attack on a golf course. Cona claimed to have taken Vioxx for two years but could only produce three prescriptions for Vioxx for those two years.²²⁵ After a five week trial and fourteen hours of deliberations, the jury awarded \$3 million to John McDarby in compensatory damages and \$1.5 million to his wife Irma, for loss of services.²²⁶ The jury, however, denied damages to Thomas Cona.²²⁷ For both plaintiffs, it was found that Merck committed consumer fraud in marketing Vioxx to doctors, Merck made misleading misrepresentations, and Merck intentionally omitted data linking

²²¹Lisa Brennan. "Over Merck objections, NJ Judge combines Vioxx cases for trial." New Jersey Law Journal. December 5, 2005.

²²²*Ibid.*

²²³*Ibid.*

²²⁴"Vioxx trial loss raises Merck strategy questions." April 6, 2006. MSNB.com. <http://www.msnbc.msn.com/id/12173094/>

²²⁵"Punitives mulled against Merck after \$4.5 million Vioxx verdict." The Legal Intelligencer. April 10, 2006.

²²⁶*Ibid.*

²²⁷*Ibid.*

Vioxx to increased risk of heart attacks.²²⁸ The decision to refuse compensatory damages to Cona was likely due to his inability to prove the length of time he took Vioxx. Following the initial trial, a three day punitive damages trial ensued to allow jurors to determine if there was “clear and convincing evidence that Merck withheld material information about Vioxx from the Food and Drug Administration and that its conduct was deliberately meant to harm.”²²⁹ The jury came to an affirmative answer on that question and awarded \$9 million to McDarby in punitive damages.²³⁰

McDarby’s attorney Robert Gorden of the New York firm Weitz and Luxemburg noted that this was the first punitive damages verdict brought down against a pharmaceutical company since the passage of New Jersey’s 1995 Product Liability Act.²³¹ Under that act punitive damages are capped at five times the compensatory damages award. Therefore the award could have been as high as \$22.5 million.

Merck attorneys claimed that at no time was improper data ever provided to the FDA. They went on to argue that the jury in the *Cona/McDarby* case was permitted to hear “irrelevant and prejudicial” information from the plaintiffs’ lawyers.²³² Merck vowed to appeal the judgment and would focus their appeal on the restrictions placed on them in presenting evidence to the jury.²³³ *Cona/McDarby* again emphasized the point that in regards to the admission of evidence, state courts would not be friendly to the Merck cause.

The decision in *Cona/McDarby* was a divided victory for both Merck and the plaintiffs’ team and it therefore did not send a clear message to either side. The verdict did, however, make several important statements in regard to future litigation. First, Merck’s initial worries over consolidation were likely valid given that

²²⁸Ibid.

²²⁹Lisa Brennan. “Jury hits Merck with \$9 million in Punitives, Finding Vioxx data withheld from FDA.” New Jersey Law Journal. April 17, 2006.

²³⁰Ibid.

²³¹Ibid.

²³²Ibid.

²³³Ibid.

the jury split its decision even though it was a case of similar facts and plaintiffs. Therefore, Merck will be better served if future cases are not consolidated. Also, the verdict indicated that there is no clear precedent regarding the issue of failure to warn.²³⁴ Merck had been cleared on that issue in two previous cases but lost on it in *Cona/McDarby*. And although Merck was slapped with punitive damages, given that the damages could have been as high as \$22.5, the \$9 million awarded does not reflect the kind of anger on the part of the jury as was seen in the *Ernst* case in Texas. The *Cona/McDarby* decision was a mixed signal for both sides and did not provide a clear path to success for future litigation.

Future Predictions for Vioxx Litigation

Merck has vowed to try each case and appeal each loss it faces in regards to Vioxx. In a recent disclosure, however, Merck revealed that the number of lawsuits it must defend has gone from 9,500 three months ago to over 11,000.²³⁵ Merck also faces a large class action lawsuit filed on behalf of health care providers, unions, and insurers suing to recover losses they incurred from purchasing the drug for employer health plans.²³⁶ Merck vows to appeal the class certification.²³⁷ At the time of the *Cona/McDarby* verdict, Merck had won two state cases (including the *Cona* verdict) and lost two. Merck also won the only federal trial thus far. In the cases it did lose, Merck was ordered to pay over \$200 million in damages to plaintiffs and their heirs.²³⁸ Yet, a large, global settlement does not seem to be on the radar screen. It seems that Merck, at this point, is still relatively confident that it can win enough cases to keep it viable. While the Merck defeats thus far have been major, their victories have sustained them. And it appears that Merck intends to continue fighting for

²³⁴“Verdict in Joint Vioxx Trial Fails to Clarify Outlook for Merck & Co.” World Market Analysis. April 6, 2006.

²³⁵“One case at a time.” Houston Chronicle. April 21, 2006. <http://www.chron.com/disp/story.mpl/business/3811649.html>

²³⁶“New Jersey appeals court upholds Vioxx class action certification.” Jurist: Legal News and Research. April 1, 2006.

²³⁷*Ibid.*

²³⁸*Ibid.*

important victories even if that means suffering through more losses.

Given the way the cases have played out thus far, Merck will be best served by carefully choosing the cases it decides to pursue and by picking favorable jurisdictions. The more cases Merck lawyers can move to federal court the better off the company will be. From the plaintiff perspective, the opposite is true. The strongest venue for plaintiffs will continue to be state courts where the rules of evidence are relaxed. The themes in the cases should remain relatively similar to those that have already been tried because, as mentioned earlier, no clear precedent has been set on any of the major issues. As always, momentum will be a key issue for both sides. To this point, the litigation score has seesawed between the two sides. In the future if the plaintiffs' bar achieves several key victories in short order, a settlement will be much more likely. Or if Merck manages such a feat, many plaintiffs will be likely to drop their claims. If however, the future cases are anything like the cases already tried, juries will continue to split between the two sides which will only prolong the litigation chapter of the Vioxx story.

Concluding Thoughts

After careful examination of the entire Vioxx story, placing blame on only one actor is difficult if not impossible. Missteps, poor judgment, and misplaced priorities plagued both Merck and the FDA. There were multiple actions by both organizations that should have been done differently.

Merck should have completed much larger and more thorough studies of Vioxx to determine specific details regarding Vioxx's safety and efficacy. Those studies should have been done prior to submitting the drug to the FDA for review and approval. Another misstep on the part of Merck happened when results of the VIGOR trial were available. Merck's claim that Vioxx's heightened cardiovascular event numbers were the

sole effect of naproxen's protective effect was merely a way of rationalizing what were clearly adverse study findings. Also, in its dealings with the FDA, Merck does not appear to have been upfront about their study findings and often waited weeks and months to make critical data available. And while Merck did voluntarily pull the drug from the market without an order from the FDA, it is arguable that the withdrawal was long overdue. To go even further it could be said that Vioxx should have never been placed on the market to begin with.

The FDA too should shoulder its share of criticism for the handling of Vioxx. As pointed out on numerous occasions during the congressional hearings on the subject, the FDA willingly reviewed and approved Vioxx on the basis of very little data and safety information. The FDA's Arthritis Committee was so pleased with the notion that the drug would lower gastrointestinal events that it all but ignored the possibility of other health consequences. The FDA should have refused to consider review of Vioxx until more extensive research was completed. If the FDA had waited for the results of the VIGOR study before accepting Vioxx for review, it might not have been approved at that time and many lives would have been saved. Also, like Merck, the FDA did not move speedily when negative results were received. From the time it received the first troubling figures regarding the increased risk of heart attack in Vioxx users, there was almost a two year delay before any warning to consumers was placed on the drug. That delay is inexcusable.

The Vioxx debacle is a situation that could have easily been avoided. As mentioned, a requirement of large and expansive studies on every drug submitted to the FDA for approval would have changed the course of the Vioxx story. Moreover, priority review should be reserved for only those drugs meant specifically

to treat life-threatening illnesses. It seems clear that the FDA has relaxed the requirements for a drug to receive expedited review and approval which is likely to hurt public safety rather than help it. Also, as suggested by several of the witnesses at the congressional hearings, an independent FDA office with the sole mission of monitoring the safety and efficacy of drugs already approved for market use would greatly reduce the likelihood of a similar situation in the future. Because the independent office would not be responsible for approving the drugs and would only monitor drugs post-approval, the conflict of interest that appears to plague the FDA now would be eliminated. In addition to these reforms there should also be improved communication between the pharmaceutical manufacturer and the FDA. In the Vioxx situation, Merck and the FDA scheduled meetings and phone calls and inevitably most were delayed or cancelled. There must be an understanding between both parties that the priority is public safety and in order to protect public safety, effective and respectful communications between the manufacturer and the FDA is critical.

The bottom line in the Vioxx saga is that an unsafe drug was put on the market and remained there long enough to affect the health and wellbeing of thousands and maybe millions of users. It was a drug that showed tremendous promise in that it would likely reduce the stomach problems similar drugs had caused in the past. That benefit was so appealing however, that Vioxx's serious flaws were ignored. It is vital to fully understand what happened in the story of Vioxx because only with full knowledge of the various mistakes and problems that took place is it possible to prevent them in the future.